REMARKS

Claims 59-86 are currently pending in the subject application. Claims 1-58 were previously canceled without prejudice. By this amendment, claim 59 has been amended, and claims 66-87 have been added to further claim Applicant's invention.

Support for the amendments to claim 59 may be found in the specification at, inter alia, page 4, lines 25-28.

Support for new claim 66 may be found in the specification at, inter alia, page 4, lines 25-28; page 5, lines 20-30; and page 6, lines 32-34.

Support for new claims 67-69 may be found in the specification at, inter alia, page 5, lines 27-30; and page 6, lines 32-34.

Support for new claim 70 may be found in the specification at, inter alia, page 5, line 21.

Support for new claim 71 may be found in the specification at, inter alia, page 5, lines 27-30; and page 6, lines 32-34.

Support for new claim 72 may be found in the specification at, inter alia, page 4, lines 25-28; page 5, lines 20-30; and page 6, lines 32-34.

Support for new claims 73-75 may be found in the specification at, inter alia, page 5, lines 27-30; and page 6, lines 32-34.

Support for new claim 76 may be found in the specification at, inter alia, page 5, line 21.

Support for new claim 77 may be found in the specification at, inter alia, page 5, lines 27-30; and page 6, lines 32-34.

Support for new claim 78 may be found in the specification at, inter alia, page 4, lines 25-28; page 5, lines 20-30; and page 6, lines 32-34.

Support for new claims 79-81 may be found in the specification at, inter alia, page 5, lines 27-30; and page 6, lines 32-34.

Support for new claim 82 may be found in the specification at, inter alia, page 5, line 21.

Support for new claim 83 may be found in the specification at, inter alia, page 5, lines 27-30; and page 6, lines 32-34.

Support for new claims 84-87 may be found in the specification at, inter alia, page 14, lines 14-17.

Applicant maintains that these amendments raise no issue of new matter.

Rejection Under 35 U.S.C. §103(a)

Claims 59-65 stand finally rejected under 35 U.S.C. § 103(a) as being unpatentable over Metcalf. On page 2 of the January 6, 2006, Final Office Action, the Examiner maintained the rejection of claims 59-64 under 35 U.S.C. § 103(a) as allegedly unpatentable over Metcalf et al. (Metcalf). The Examiner alleged that Metcalf teaches a method of using oxandrolone for nitrogen retention wherein the daily amounts of oxandrolone are from 5 mg, 10 mg, 20 mg, and up to 150 mg. The Examiner also alleged that oxandrolone was taken as a single dose daily, referring to page 60 of Metcalf, and that Metcalf teaches that the optimal dosage is 25 mg or 30 mg a day.

Metcalf is a 1965 study of the effects of oxandrolone therapy on nitrogen retention that the Office Action alleges discloses

daily oxandrolone doses of 5, 10, 20 and 150 milligrams. Office Action at 2. The Office Action argues that Metcalf allegedly suggests its use for HIV-positive patients and patients suffering from chronic illness. *Id.* Applicant respectfully traverses the Examiner's obviousness rejection and maintains that the presently pending claims are not obvious over Metcalf. As explained hereinafter, Metcalf fails to teach or suggest the claimed invention for at least three reasons.

First, Metcalf is inapplicable to the claimed invention because the study therein specifically excluded patients with nitrogen-sensitive disorders, such as patients suffering from chronic human immunodeficiency virus type-1 infection, as recited in the pending claims. Second, Metcalf teaches away from using oxandrolone in the claimed dosages due to its admitted ambiguous results and poor performance. Third, Metcalf does not disclose or suggest single doses of oxandrolone of specific amounts.

I. Metcalf specifically excludes the relevant class of patients.

Metcalf fails to teach or suggest the claimed invention because it expressly excludes the category of patients recited in the pending claims - namely, patients suffering from myopathy, weight loss, or muscle wasting resulting from chronic human immunodeficiency virus type-1 infection. In particular, page 60 of *Metcalf* expressly states the types of patients excluded from the study:

> Patients with diseases or conditions <u>not</u> affecting nitrogen metabolism were the subjects of this experiment. (Emphasis added).

It is well known in the art that myopathy, weight loss, or muscle wasting resulting from chronic human immunodeficiency virus type-1 infection in patients, affect the patients' nitrogen metabolism thereby resulting in nitrogen depletion. (e.g.

specification at page 6, lines 16-17; Dunn, J.M. (1998) "Nutritional Abnormalities in HIV/AIDS," HIV Hotline, Vol. 8, No. 2, page 11-2; or Kotler, D.P., (2000) "Body Composition Studies in HIV-Infected Individuals," Ann. NY Acad. Sci., Vol. 904, pp 546-552.)

As a result, a person skilled in the art would not understand the *Metcalf* study, which **intentionally excluded** patients with abnormal nitrogen metabolism, to teach that the results are applicable to such an excluded group. Thus, care and concern for the patient's health would compel a person skilled in the art not to treat patients suffering from myopathy, weight loss, or muscle wasting resulting from chronic human immunodeficiency virus type-1 infection with oxandrolone unless there was evidence of oxandrolone's usefulness and safety in such patients.

Indeed, *Metcalf* provides no such teaching – but the present application does provide such teaching. Therefore, Applicant respectfully asserts that *Metcalf* does not teach or suggest the use of oxandrolone as recited in the pending claims.

II. *Metcalf* admits to poor and ambiguous results regarding effective doses of oxandrolone.

In addition to the intentional exclusion of nitrogen-depleted patients from *Metcalf*, Applicant also maintains that *Metcalf* teaches away from the claimed invention because it discloses that the nitrogen retention for patients taking oxandrolone is at best ambiguous and, in fact, is less effective in patients taking the presently claimed dosages.

As known in the art and explained above, nitrogen retention is a measure of therapeutic success in patients suffering from muscle wasting, myopathy, and low body weight from chronic human immunodeficiency virus type-1 infection. Thus, while the Examiner correctly points out that *Metcalf* discloses oxandrolone at doses

from 5, 10, 20 and up to 150 milligrams per day (Office Action at 2), *Metcalf* expressly admits that the effect of such dosages were completely not understood –the researchers were "uncertain which of the dose responses to include in the final analysis because of the variable response at low dose levels." *Metcalf* at 60.

In addition to these ambiguous results, *Metcalf* described that oxandrolone was less useful for improving nitrogen retention at virtually all dosage levels. *Metcalf* at 61. For example, *Metcalf* described "[t]he mean retention ratio of the 12 low dosage trials was 20.1 per cent and of the 15 trials at 30 mg. and above was 23.8 per cent," which *Metcalf* described as "highly" statistically significant. *Metcalf* at 61. Such low nitrogen retention for oxandrolone patients (i.e., only a small improvement on nitrogen retention for larger doses of oxandrolone) plainly does not suggest use of oxandrolone in patients suffering from nitrogen depletion, as do the patients recited in the pending claims. Claim 60 of the present application, for example, recites the administration of oxandrolone in 7.5-20 milligram doses to patients suffering from chronic human immunodeficiency virus type-1 infection. According to *Metcalf*, however, nitrogen retention levels were not even optimal in that dosage range of oxandrolone. *Metcalf* at 63.

Therefore, Applicant respectfully asserts that rather than suggesting an effective treatment using low doses, or any doses, of oxandrolone, *Metcalf* actually teaches away from the claimed invention because the nitrogen retention results of Metcalf were erratic and further, treatments under the "optimum" dosage levels of 25 milligrams did not help patients retain nitrogen. As a result, a person skilled in the art would understand *Metcalf* as teaching that oxandrolone treatment in the claimed dosage levels, in particular 20 milligrams and lower, for patients suffering from nitrogen depletion is simply ineffective. Applicant respectfully asserts that it is the present application which provided evidence of the usefulness of oxandrolone in treating patients with

disorders affecting nitrogen retention, such as patients suffering from myopathy, weight loss, and muscle wasting resulting from chronic human immunodeficiency virus type-1 infection.

According to §2143 of the MPEP, in order to establish a prima facie of obviousness, the Examiner must show, *inter alia*, that a reasonable expectation that the allegedly obvious invention would succeed. *See also Medichem v. Rolabo*, 437 F.3d 1157, 1162 (Fed. Cir. 2006). This standard clearly is not met here. One of ordinary skill in the art would not read *Metcalf* and surmise that the claimed invention could be successful. Instead, *Metcalf*'s ambiguous results and ranges of unpredictable effectiveness would suggest to one skilled in the art that Applicant's claimed invention would result in an unsuccessful nitrogen retention medication. Accordingly, Applicant respectfully submits that the independent claims are neither taught nor suggested by *Metcalf*. Finally, because the dependent claims are each respectively dependent upon one of independent claims, they also are patentable over *Metcalf* for the same reasons.

III. *Metcalf* does not disclose single-dose compositions of greater than 2.5 milligrams.

The Examiner also has not shown that Metcalf discloses a pharmaceutical composition containing more than 7.5 mg of oxandrolone in a single unit dose. In fact, as explained in further detail below, in 1965, the only approved oxandrolone formulation was ANAVAR®, which was available only in 2.5 mg unit doses.

Metcalf refers to a daily "dosage" but does not indicate that the daily "dosage" was available as a single dosage unit or single pill.

Implicitly acknowledging the fact that this claim element is missing from the *Metcalf* reference, the Examiner alleged 1) that applicant has not provided "clear and direct" evidence that *Metcalf*

used the dosage form on the market at that time, and 2) that *Metcalf* does not state whether the daily dosage is composed of multiple pills. However, the burden is not on Applicant to present evidence as to whether a claim element missing from a prior art reference was otherwise known at the time of the reference. Rather, the initial burden of factually supporting an obviousness rejection rests on the Examiner, not the applicant. Nevertheless, Applicant has provided "clear and direct" evidence that *Metcalf* does not support the Examiner's assertions.

Notably, Examiner explicitly acknowledged that *Metcalf* does not state whether multiple pills or a single dosage was administered. This uncontested fact, by itself, necessitates withdrawal of the rejection for failing to establish every element of the claims (i.e., that the oxandrolone was administered in the form of a single unit dose with the claimed dosage level of oxandrolone present in a single unit).

Moreover, a person skilled in the art would necessarily understand *Metcalf* as using multiple pills to achieve the daily dosage level. The disclosure of *Metcalf* specifically states that its research was financially supported by G.D. Searle and that the oxandrolone used was produced and provided by G.D. Searle. The footnote on page 59 of Metcalf states: "This investigation was supported by a grant from G.D. Searle and Co." The footnote also discloses that the oxandrolone used was "Synthesized by Dr. Rapheal Pappo, Division of Chemical Research, G.D. Searle and Co." On page 66, *Metcalf* further states: "We are grateful for the support of these studies from G.D. Searle and Company ...."

The only oxandrolone formulation available to the public in 1964 from G.D. Searle and Co. was ANAVAR® tablets, each containing 2.5 mg of oxandrolone. See pages 1 and 15 of the Physician's Product Brochure No. 43 for ANAVAR® Brand of Oxandrolone, which the applicant previous submitted in the Fourth Supplemental Information

Disclosure Statement dated October 11, 2005.

It is notable that Metcalf only administered dosages which are multiples of 2.5 mg, i.e. 2.5, 5, 10, 20, 40, 80 and 150 mg/day. As noted above, oxandrolone was only available at the time of the reference in the form of 2.5 mg tablets.

In summary, the Examiner has not provided any factual support to contest the likelihood that *Metcalf* used tablets containing 2.5 mg of oxandrolone. Instead, the January 6, 2006, Final Office Action attempts to shift the burden to applicant to prove that *Metcalf* did not use a single dose. As explained previously, the attempt to shift the burden to Applicant is contrary to the requirements of a proper *prima facie* obviousness rejection, which mandate that the Examiner must first set forth facts for asserting that Metcalf did use a single dose.

Accordingly, applicant maintains that *Metcalf* did not administer oxandrolone as a single unit dose in the dosage strength range set forth in Applicant's current claims. Therefore, *Metcalf* does not disclose all the elements of the pending claims.

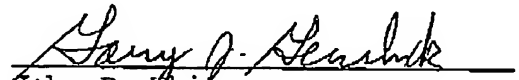
Conclusion

For each of the above reasons, independently discussed above, applicant respectfully submits that all pending claims of the subject application are patentable over *Metcalf*. Withdrawal of Examiner's rejections and allowance of the currently pending claims are respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than $450.00 fee for a two-month extension of time and the $650.00 excess claim fee, is deemed necessary in connection with the filing of this Amendment. Authorization is hereby given to charge the amount of such fees and any other fees that may be due to Deposit Account No. 03-3125.

Respectfully submitted,



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